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SYSTEMATIC REVIEW

The Safety of Alcohol Pharmacotherapies in Pregnancy: A Scoping Review of Human and Animal Research

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Abstract

Background and Objective Alcohol pharmacotherapies pose unknown teratogenic risks in pregnancy and are therefore recommended to be avoided. This limits treatment options for pregnant individuals with alcohol use disorders (AUD). The information on the safety of these medications during pregnancy is uncertain, prompting a scoping review. The objective of this review was to investigate available information on the safety of alcohol pharmacotherapies in pregnancy.

Methods Studies published between January 1990 and July 2023 were identified through searches in BIOSIS, Embase, PsycINFO and MEDLINE databases, using terms related to pregnancy and alcohol pharmacotherapies. The alcohol pharmacotherapies investigated were naltrexone, acamprosate, disulfiram, nalmefene, baclofen, gabapentin and topiramate. Studies were screened by two independent reviewers. Covidence software facilitated the management, screening and extraction of studies.

Results A total of 105 studies were included in the review (naltrexone: 21, acamprosate: 4, disulfiram: 3, baclofen: 3, nalmefene: 0, topiramate: 55, gabapentin: 32) with some studies investigating multiple medications. Studies investigating naltrexone's safety in pregnancy focussed on opioid use disorders, with limited evidence regarding its safety in the context of AUD. Despite concerns about higher rates of some pregnancy complications, studies generally indicate naltrexone as a safer option compared with opioid agonists or alcohol during pregnancy. Acamprosate was not clearly associated with adverse effects of exposure in pregnancy, with two pre-clinical studies suggesting potential neuroprotective properties. Disulfiram has a high risk of congenital anomalies when used in pregnancy, believed to be due to its mechanism of action. Prenatal topiramate has also been associated with an increased risk of congenital anomalies, particularly oral clefts. There were mixed results concerning the safety of prenatal gabapentin and little to no literature investigating the safety of baclofen or nalmefene during pregnancy.

Conclusions There is insufficient research on the safety of alcohol pharmacotherapies in pregnancy. Despite this, given alcohol's teratogenic effects, naltrexone could be considered to help maintain abstinence in pregnant individuals with AUD, particularly when psychosocial treatments have failed.

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Key Points

There is insufficient research on the safety of alcohol pharmacotherapies in pregnancy.

Further research is essential to understand the potential benefits or risks associated with alcohol pharmacotherapy use in pregnancy.

Despite this, given alcohol's teratogenic effects, naltrexone could be considered to help maintain abstinence in pregnant individuals with alcohol use disorders, particularly when psychosocial treatments have failed.

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1 Background

Globally, alcohol use disorders (AUD) are the most common substance use disorder among females, affecting 29.5 million females globally [1]. There are a number of approved pharmacotherapies used for the treatment of AUD including naltrexone, acamprosate, disulfiram, nalmefene, and baclofen, as well as repurposed medications topiramate and gabapentin [2]. Emerging use of pharmacotherapies [3], the development of long-acting implant preparations [4], and high unintended pregnancy rates among females who use alcohol and other drugs [5–7] mean inadvertent foetal exposure to alcohol pharmacotherapies is probable. Additionally, alcohol pharmacotherapies could play an important role in reducing alcohol consumption during pregnancy, and therefore reduce extensive teratogenic effects [8, 9].

However, the use of these pharmacotherapies in pregnancy is typically not recommended due to the unknown foetal risks and lack of evidence regarding safety and efficacy. There is a lack of agreement between health organisation guidelines for the pharmacological management of AUD in pregnancy. Multiple guidelines recommend that relapse prevention medications should not be initiated in pregnant individuals [11–14] due to the low level of evidence [13]. Although, many also state that if the patient is already established on an alcohol pharmacotherapy prior to conceiving, they should be considered on a case-by-case basis where potential risk to the foetus from the medication is balanced against the risk of return to alcohol use [10–12]. The World Health Organization (WHO) state, for example, that "given the safety and efficacy of medications for the treatment of alcohol dependence has not been established in pregnancy, an individual risk benefit analysis should be conducted for each woman" [10].

The extent of available information in the literature regarding the safety of these medications in pregnancy remains uncertain. To address this, a scoping review was conducted with the aim of systematically evaluating the full breadth of research in this area, as well as highlighting any gaps in knowledge. To provide insight into the effects of various alcohol pharmacotherapies in pregnancy, we reviewed a wide range of literature, encompassing both clinical and non-clinical research. Evaluating the safety of alcohol pharmacotherapies in pregnancy will aid in determining the safest pharmacological options for the management of AUD during pregnancy.

2 Methods

This scoping review aimed to find literature on the safety of alcohol pharmacotherapies in pregnancy. The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist [15]. Alcohol pharmacotherapies included in this review consist of US Food and Drug Administration (FDA), Australian Therapeutic Goods Administration (TGA), European Medical Association (EMA), and/or French National Agency of Medicine (ANSM) approved medications (naltrexone, acamprosate, disulfiram, nalmefene, baclofen), as well as some medications commonly repurposed for the treatment of AUD (gabapentin, topiramate). We identified studies by searching BIOSIS Previews, Embase, APA PsycInfo and Ovid MEDLINE encompassing literature published from January 1990 to July 2023 (Online Resource S1). The scoping review was prospectively registered at Open Science Framework on 3 August 2022 [16].

Studies were eligible for inclusion if the population involved patients or animals exposed to one of the medications of interest during pregnancy/prenatal development, they were written in English, and they were primary research studies (including quantitative epidemiological studies, cohort studies, case-control studies, randomised control trials, and in vivo animal studies). Studies were excluded if they were case reports, reviews, qualitative research, in vitro animal studies, conference abstracts, the medications were not used in pregnancy, the medications were used in a polytherapy regimen (where results were not separated from monotherapy regimens, or majority of participants were not on monotherapy), the study sample size was less than ten (although studies with small population numbers have been discussed, where no other literature is available) and no statistical comparisons were made. Studies were not restricted based on the comparator.

Databases were searched using Ovid Technologies, with identified studies downloaded into EndNote [17]. EndNote functions were used to remove duplicate records, with remaining studies uploaded to Covidence systematic review software [18] where any missed duplicates were removed. Two reviewers independently screened titles and abstracts of identified studies to determine if they met the inclusion criteria. Subsequently, full-text screening of likely eligible studies were independently reviewed by the two reviewers and conflicts were resolved via discussion. Data charting was conducted independently in Covidence and extracted to Microsoft Excel. Information collected included the medication name, article characteristics (e.g. first author, year of publication etc.), study design, comparison group and outcome measures (such as pregnancy loss, congenital anomalies, birth weight etc.). Data were arranged in table format to summarise study outcomes (Online Resource S2 and S3).

3 Results

We identified a total of 105 published papers reporting maternal, pregnancy and/or neonatal outcomes after exposure to the alcohol pharmacotherapies of interest during pregnancy (Fig. 1). There was a total of 61% ($n = 64$) clinical studies and 39% ($n = 41$) animal studies. Studies were mostly performed in North America (32.4%), Australia (21.0%) and Europe (21.0%). The medication most commonly researched in the included articles was topiramate (Table 1).

3.1 Naltrexone

3.1.1 Clinical

A small amount of clinical research ($n = 8$) has examined the safety of naltrexone in pregnancy; however, all studies investigate the treatment of pregnant women with opioid use disorders [19–26] and not AUD. The largest of the studies prospectively evaluated the maternal and foetal effects of naltrexone as a treatment for opioid use disorder in a cohort of 121 pregnant patients [25]. When compared with neonates exposed to methadone or buprenorphine, naltrexone exposed neonates had a significantly lower rate of neonatal abstinence syndrome (NAS) and associated hospitalisation, with all other outcomes largely comparable. A smaller study was in agreement, with no NAS diagnoses among naltrexone-exposed infants, and a shorter length of stay compared with buprenorphine-exposed infants [26]. Another study of 68 mother–child dyads found that females who conceived while on naltrexone treatment had significantly higher birth rates compared to non-opioid dependent controls [22]. Additionally, females exposed to naltrexone during pregnancy had higher rates of ectopic pregnancy and pregnancy and labour complications [22]. However, the authors suggest this increased occurrence of ectopic pregnancies reflects the higher birth rate in the naltrexone treated group. Additionally, naltrexone exposed neonates were smaller (birth weight and body length), had longer hospital stays and had higher rates of urogenital birth defects [23], while in childhood they had elevated rates of hospital and emergency department presentations, and middle ear infections (otitis media) compared with non-exposed children [24]. Lastly, two case series with a combined 18 cases of implant naltrexone exposure during pregnancy found normal obstetric and birth outcomes [19, 21], as did a brief communication reporting 17 pregnancies with implant naltrexone treatment [20]. It should be noted that some of these cases also appear in the population of Kelty et al.'s (2017) retrospective cohort study [23]. It is important to bear in mind some of these differences in results may be due to other factors associated with illicit opioid use. Patients who are opioid dependent and commenced treatment during pregnancy likely underwent opioid withdrawal while pregnant. While the impact opioid withdrawal has on pregnancy is not well understood, it may impact maternal and foetal health outcomes [27].

3.1.2 Pre-clinical

The 13 animal studies identified which investigate the health effects of naltrexone use during pregnancy have yielded inconsistent results [28–40]. Importantly, these animal studies almost exclusively use models of opioid use disorders (1 out of 13) rather than AUD. In these pre-clinical trials, the effects of naltrexone on maternal and neonatal outcomes appear to depend on the dose and frequency of administration. Rat models of high human equivalent daily doses [50 mg/kg, intraperitoneal (i.p.) injections] of maternal naltrexone throughout gestation resulted in elevated birth weight by 8–14% [34–36] and crown-rump length [35], with no effects on gestation length or litter size [34, 35]. Youngentob et al. (2012) [39] also found 15% elevated bodyweight of prenatal naltrexone exposed offspring, weighed between postnatal day 12 and postnatal day 14. In addition, relative organ weights (heart, liver, and skeletal muscle) at postnatal day 21 were increased by gestational naltrexone exposure [34, 35]. Moreover, naltrexone-exposed offspring weighed 8.2–36% more than their control counterparts at postnatal day 21 [35, 36, 40] and 16.3–24.3% at postnatal day 30 [40]. In contrast, rat offspring born to mothers treated with a clinically relevant low-dose sustained-release naltrexone implant (25 mg) during gestation displayed reduced birth weight, increased litter size, and no alterations to brain morphometry in 8-week-old offspring [30].

Two studies have investigated the effects of naltrexone exposure during pregnancy on the timing of parturition [31, 32]. In a pig model, a single intravenous injection of low-dose naltrexone (1mg/kg) administered in late gestation did not delay the onset of parturition relative to saline controls [31]. However, Javadi-Payder et al. (2009) reported that a single i.p. injection of naltrexone in mice at gestation day 15 had a dose dependent response on the duration of gestation and preterm delivery. A dose of 5 mg/kg produced no changes in preterm delivery incidence; however, a dose of 10 mg/kg marginally decreased gestational days in comparison with saline control mice [32].

Research has revealed intriguing insights into the impact of prenatal naltrexone exposure on physiological, behavioural and reproductive development in rat models. Mclaughlin et al. (1997) found that pre-natal naltrexone exposed rats (50 mg/kg/day, maternal i.p. injection, high human equivalent dose) had accelerated physical and behavioural maturation compared to controls [36]. Similarly, Cohen et al. (1996) reported that daily ad libitum (40 mg/

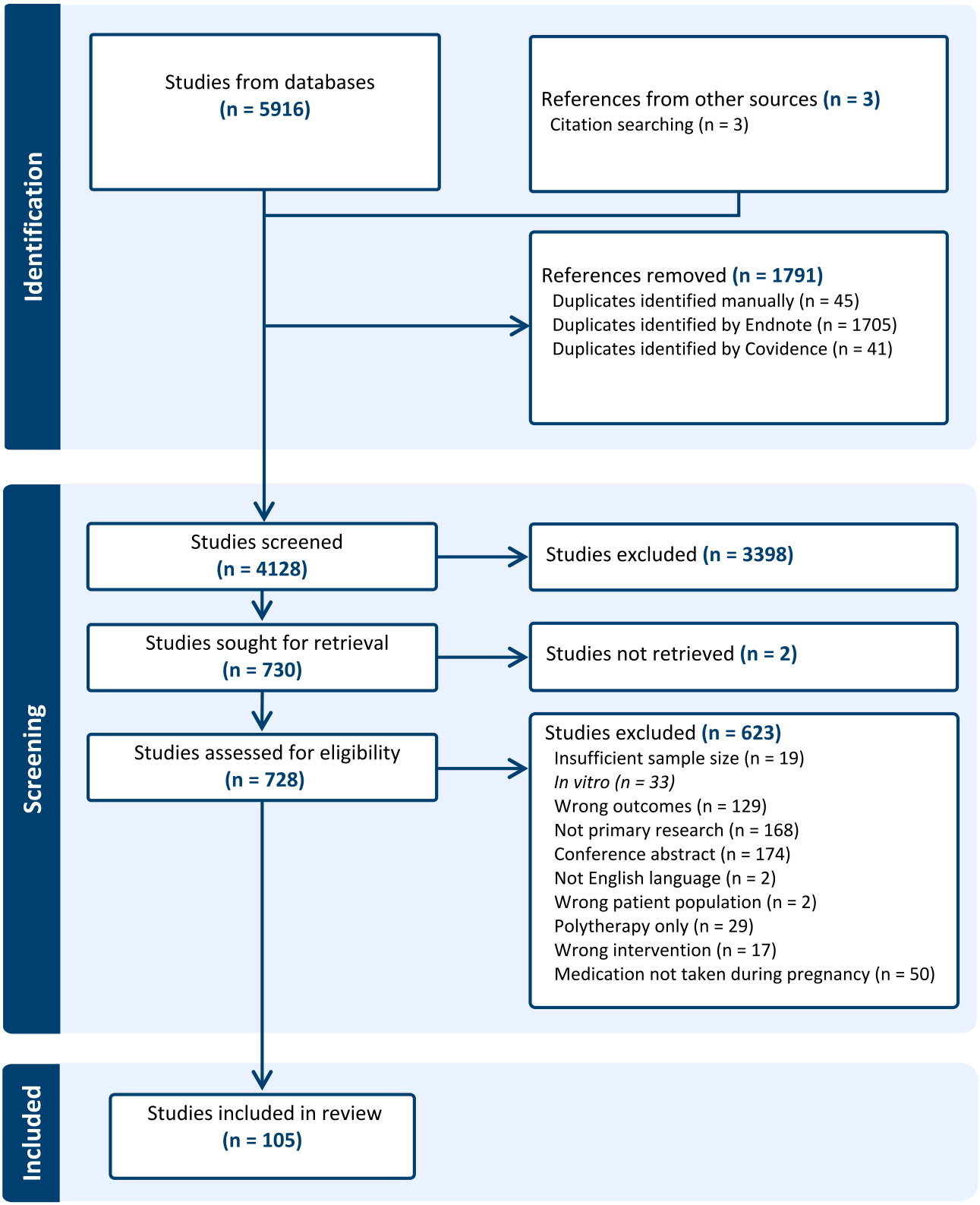

Fig. 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart for the selection of studies included in the review

Table 1 Characteristics of included studies.

Characteristic	Number	Percentage
Year of study publication		
1990–1999	10	9.5%
2000–2009	22	21.0%
2010–2019	53	50.5%
2020–mid 2023	20	19.0%
Study location		
Australia	22	21.0%
East Asia	3	2.9%
South Asia	5	4.8%
Europe	22	21.0%
North America	34	32.4%
South America	1	1.0%
North Africa and Middle East	16	15.2%
Worldwide	2	1.9%
Study design		
Animal study	41	39.0%
Cohort	56	53.3%
Case–control	2	1.9%
Cross-sectional	1	1.0%
Case series	5	4.8%
In patients with AUD		
AUD context	4	3.8%
No AUD context	101	96.2%
Medication*		
Naltrexone	21	17.8%
Acamprosate	4	3.4%
Disulfiram	3	2.5%
Nalmefene	0	0.0%
Baclofen	3	2.5%
Gabapentin	32	27.1%
Topiramate	55	46.6%

AUD alcohol use disorders

*Numbers exceed total number of included papers due to 13 clinical studies which investigated both topiramate and gabapentin pharmacotherapies; percentages may not add to exactly 100% as a result of rounding. Worldwide is more than five countries from different continents

kg) pre-natal naltrexone given in drinking water accelerated masculine sexual behaviour, but suppressed female receptivity [29]. Furthermore, Cajú et al. (2011) demonstrated that in utero naltrexone exposure (50 mg/kg/day, i.p. injection) from mid to late gestation impacted male testicular development, resulting in a reduction in the total length of seminiferous tubules and Sertoli cell population, but having no effect on sperm production [28].

The impact of prenatal naltrexone exposure on locomotor activity in rats presents mixed results. Rats administered a daily dose of 50 mg/kg throughout gestation exhibited reduced motor activity at postnatal day 21 [36]. In contrast, rats subjected to a slightly lower dose (40 mg/kg) for a shorter duration (from gestation day 13 until parturition) showed no changes in motor development during early prenatal life [29]. Adding further complexity, locomotor activity increased in mice prenatally exposed to 10 mg/kg naltrexone [33, 37] daily from late gestation (implant) [33] and twice daily from gestational day (GD) 1 to post-partum day 21 (subcutaneous injection) [37]. The reasons for these discrepancies remain unclear, and further investigation is needed to determine whether differences in rodent species, naltrexone dosage, route of administration, or duration of exposure coinciding to different stages of development contribute to the varied outcomes.

Examining broader neuronal effects, one rat study showed that continuous naltrexone exposure via a minipump throughout gestation and the early pre-natal period increased brain cortical thickness and reduced neuronal packing density in the offspring [38]. However, this exposure had no effect on neuronal number, suggesting that naltrexone exposure during development enhances neuronal maturation specifically in the brain cortex. Another rat study examined naltrexone's neuroprotective effects on olfactory development after prenatal alcohol exposure [39]. Naltrexone mitigated the heightened behavioural response to the odour of ethanol observed in prenatal alcohol-exposed offspring, suggesting a potential neuroprotective effect of prenatal naltrexone exposure on olfactory development [39].

3.2 Acamprosate

3.2.1 Clinical

There has been very little investigation into the safety of acamprosate in pregnancy [41–43], with clinical research limited to a single retrospective cohort study, and one small case series [42, 44]. In the cohort study of 52 women and their exposed neonates, acamprosate use during pregnancy was not associated with poor maternal or neonatal health outcomes when compared with pregnant women with a recent history of problematic alcohol use and those from the general community [42]. The study revealed no stillbirths or neonatal deaths, and there were no differences in rates of low birth weight, pre-term birth, or congenital abnormalities between the groups [42]. The small case series by the Teratology Information Service in France examined 18 pregnancies involving first trimester acamprosate exposure [44]. These 18 pregnancies resulted in two spontaneous abortions, three elective abortions, one therapeutic abortion (major malformations), ten unremarkable neonates (one premature, one died of sudden infant death syndrome) and two neonates with birth anomalies (one with minor facial anomalies and one with cleft lip) [44]. However, concurrent exposure to

alcohol and other drugs occurred in several cases, confounding results.

3.2.2 Pre-clinical

In a mouse model of AUD from our group, exposure to acamprosate at approximate therapeutic doses (1.6 g/L in drinking water, ad libitum) from prior to pregnancy until postpartum day 7 demonstrated no adverse effects on maternal and birth outcomes, neonatal outcomes, or neurodevelopmental markers [43]. There were also no impacts on offspring motor control, locomotion or anxiety; however, the effects on short-term memory remained uncertain. Notably, the study provided preliminary evidence to suggest that acamprosate displayed neuroprotective effects against damage caused by in utero alcohol exposure. This finding is supported by another non-clinical study whereby hamsters prenatally exposed to acamprosate (1.33 g/L or 6.0 g/L, ad libitum; GD 5/8 to postnatal day 6) and/or ethanol demonstrated that acamprosate prevented the neuronal cell damage and death (measured via lesion size) caused by alcohol exposure [41].

3.3 Disulfiram

3.3.1 Clinical

There were no clinical studies reporting disulfiram exposure during pregnancy within our search criteria. This lack of recent research is likely attributable to research in the late 1970s and 80s in which the use of disulfiram in pregnancy was associated with an increased risk of poor neonatal health outcomes including congenital anomalies [45–47]. In these reports, as summarised by Briggs et al. (2017), there were 38 foetuses (36 pregnancies) prenatally exposed to disulfiram of which 11 (28.9%) had congenital anomalies. Additionally, there were 6 elective terminations, 1 spontaneous abortion, 1 stillbirth, 14 unremarkable newborns and 5 lost to follow-up [44]. These outcomes must be interpreted with caution due to concurrent exposure to alcohol occurring in many of these pregnancies. Briggs et al. (2017) identified a further 25 neonates with in utero disulfiram exposure (via personal communication) whereby a major birth abnormality occurred in one neonate (4.0%) [44].

3.3.2 Pre-clinical

The three pre-clinical studies on disulfiram exposure in pregnancy included in this review present conflicting findings [48–50]. In guinea pigs administered oral disulfiram tablets (125 mg/kg) for 3 days late in pregnancy, there was no impact on litter size, incidence of spontaneous abortion or mean body weight of offspring. However, female offspring exposed to disulfiram exhibited smaller brain weights compared with controls, but not in male offspring [48]. In pregnant mice, a single dose (75 mg/kg, i.p. injection) of disulfiram on GD9 resulted in offspring with limb deformities including forelimb defects and postaxial ectrodactyly [49]. In contrast, some benefits were noted in mice exposed to disulfiram for the first three days of pregnancy at a smaller dose (50 mg/kg) via oral gavage [50]. This exposure increased the degree of vascularisation and volume of uterine horns, potentially providing a better environment for embryo implantation. Additionally, there were no differences in litter size and birth weight compared with control offspring.

3.4 Baclofen

3.4.1 Clinical

Information on the safety of baclofen in pregnancy is extremely limited, with no studies identified congruent with our inclusion criteria. However, a single case series of 3 women and 4 pregnancies exposed to an intrathecal baclofen pump was identified. These cases reported no maternal adverse effects except for one instance of pre-eclampsia [51]. There was some variation in neonatal outcomes, with one infant small for gestational age, one large for gestational age. The remaining two infants were appropriate size for gestational age; however, they were both born premature and admitted to the special care nursery. No infants were reported to have evidence of teratogenicity or neurologic complications at birth, however two of the infants were diagnosed with jaundice.

3.4.2 Pre-clinical

Three pre-clinical studies investigated baclofen exposure in pregnancy, one focussing on maternal behaviour outcomes [52], and the other two on foetal effects [53, 54]. In the maternal behaviour model, rats injected intracerebrally with a single dose of baclofen (200 ng) late in pregnancy displayed reduced maternal care behaviours as demonstrated by lower quality nest building, longer latency for pup licking, and reduced pup retrieving compared to saline controls [52]. In the two studies examining rat foetal outcomes, both found that in utero baclofen exposure (30 mg/kg via i.p. injection) altered neural tube formation, widening the vertebral arch of the foetuses [53, 54]. These findings indicate a risk of spina bifida and other neural tube defects in neonates exposed to baclofen in utero.

3.5 Nalmefene

No human or animal studies investigating the safety of nalmefene in pregnancy appeared in our literature search.

3.6 Topiramate

3.6.1 Clinical

The safety of topiramate use during pregnancy has been a subject of much investigation with 44 clinical studies conducted, but none with an AUD lens. A considerable focus of this research has been the identified elevated risk of congenital anomalies among children prenatally exposed to topiramate [55–67], with particular concern for oral clefts [56–58, 61, 62, 68–70] and hypospadias [58, 63, 64, 68]. However, not all studies have identified an increased risk of congenital anomalies [70–84] or oral clefts associated with topiramate monotherapy exposure [65, 71, 81]. Cohen et al. (2019) found a crude increase in the risk of ischemic placental disease, preeclampsia, placental abruption, small for gestational age, or preterm birth when compared with unexposed pregnancies; however, following adjustment for confounding, these differences were no longer apparent [85].

Multiple studies have found an adverse association between topiramate exposure and foetal growth [60, 74, 83, 86–88]. Additionally, Trivedi et al. (2018) found an increased risk of spontaneous foetal loss associated with topiramate monotherapy [89]. However, Sarayani et al. (2023) found no increased fertility rate associated with topiramate use [90], and Vajda et al. (2018) found no increased risk of intrauterine foetal death for topiramate monotherapy compared to unexposed pregnancies [91].

Prenatal topiramate exposure has also been associated with an increased risk of poor neurodevelopmental outcomes [60, 92] and intellectual disabilities including autism spectrum disorder [93], learning disabilities [94] and attention-deficit hyperactivity disorder (ADHD) [95]. In contrast, other studies found no increased risk of neurodevelopmental disorders [96, 97] or reduced cognitive abilities [98].

3.6.2 Pre-clinical

Pre-clinical models have also demonstrated an increased risk of congenital anomalies. Mishra et al. (2008) observed that offspring of rats exposed to topiramate (40 mg/kg, 100 mg/kg or 200 mg/kg, oral intubation) from GD 9–12 had no change in foetal weight; however, foetal anomalies were observed in all treatment groups. Such anomalies consisted of growth restriction and limb deformities, as well as bone deformities [99]. Likewise, in a similar rat model of exposure (40 mg/kg, 100 mg/kg or 200 mg/kg) from GD9–12, foetuses showed no reduction in weight or size; however, various limb and bone anomalies were observed [100]. Foetal rats prenatally exposed to topiramate at equivalent human therapeutic doses (50 mg/kg or 100 mg/kg, intragastrically, GD9–19) had delayed ossification of ribs and vertebrae and an increase in skeletal abnormalities (particularly in the ribs) [101]. Foetal weight was also reduced, with no corresponding reduction in maternal weight gain. In other rodent models, intragastric topiramate exposure (50 mg/kg, 100 mg/kg) from mid to late pregnancy induced symmetrical intrauterine growth restriction (significantly reduced foetal weight, crown-rump length, head length and biparietal diameter) in rat foetuses at both doses [102]. Another study employing a substantially lower dose (8.4mg/kg, oral) reported various lesions in foetal mouse kidneys after prenatal exposure until GD18 [103].

Multiple rat studies have demonstrated placental changes with exposure to topiramate in pregnancy at various doses (40–200 mg/kg). There were reported pathological changes such as haemorrhages and deposition of the fibrinoid resulting in a thicker placental barrier (exposure from GD 9–12) [99], degenerative changes in all placental layers (exposure from GD 6–19) [104], gross abnormalities (exposure from GD 6–19) [102] and an increase in placental weight with histology displaying further structural alterations in the basal layer and labyrinth zone (exposure from GD 5–19) [105].

Zebrafish models have also provided insights into the adverse effects of topiramate exposure [106, 107]. One study revealed impaired oogenesis in the maternal reproductive system, and offspring with bone dysplasia and cartilage malformations in the craniofacial area at a dose equivalent to the maximum recommended in humans (0.5 mg/g/day, ad libitum fish food) [106]. Similarly, research by Lee et al. (2013) further supported these findings by reporting malformations (heart oedema, yolk deformity and scoliosis) in zebrafish embryos exposed from the initiation of gastrulation until the termination of hatching [107].

Contrastingly, a rat model examining topiramate exposure at a dose of 10 mg/kg (i.p. injection) later in pregnancy (GD 14–19) demonstrated no significant impact on maternal weight gain, the number of pups born, or pup mortality [108]. Furthermore, this study indicated that prenatal topiramate exposure did not adversely affect brain development in rat offspring [108], standing in contrast to another study of a higher dose (25 mg/kg, i.p. injection) that suggested cognitive impairment in rats prenatally exposed to topiramate in the first and third trimesters, manifesting as deficits in spatial learning and memory [109].

3.7 Gabapentin

3.7.1 Clinical

Our search identified 23 studies reporting clinical outcomes associated with gabapentin use during pregnancy, with none of these studies investigating gabapentin in an AUD context. The largest population-based study (n = 9418 exposed to gabapentin) found a 49% increased risk of major congenital anomalies and 77% increased risk of cardiac anomalies, with first trimester maternal gabapentin exposure, however, following adjustment for confounders (e.g. maternal age, ethnicity, indication for gabapentin, other conditions, use of opioids etc), these differences were no longer apparent [110]. Gabapentin use in early pregnancy was associated with a 17% increased risk of preeclampsia and 71% increased risk for small for gestational age neonates, while use late in pregnancy was associated with a higher risk of preterm birth by 28%, small for gestational age by 39%, and neonatal intensive care unit (NICU) admission by 112% in the adjusted model [110]. Fujii et al. (2013) similarly found no increased risk of birth anomalies associated with first trimester gabapentin exposure; however, they found that gabapentin increased the risk of preterm birth and low birth weight (<2500 g), and the need for NICU admission [111]. This was consistent with findings by Mostacci et al. (2018), who observed that newborns exposed to gabapentin throughout pregnancy were more likely to be born preterm and small for gestational age compared to unexposed newborns [112]. Likewise, Kilic et al. (2014) found that prenatal gabapentin exposure was associated with a reduction in gestational age at birth, although there was no link to low birthweight or small for gestational age [88]. Two smaller population-based cohort studies concluded that gabapentin exposure during pregnancy did not lead to an increased risk of adverse foetal events or birth anomalies [68, 72]. Other studies with smaller sample sizes support these results [57, 65, 73, 81, 83, 91, 113–115]. Moreover, studies investigating the impact of prenatal gabapentin exposure on child neurodevelopmental disorders suggest no heightened risks [93, 94, 96, 97]. Interestingly, while gabapentin itself has not been associated with NAS, its use in pregnancy alongside opioids has been associated with an increased risk of NAS [116–119].

3.7.2 Pre-clinical

Pre-clinical studies investigating the impacts of gabapentin exposure in pregnancy have yielded predominantly adverse outcomes. While one study reported no evidence of teratogenicity in mice, rats or rabbits at gabapentin doses ranging from 60 to 3000 mg/kg through mid-gestation [120] and another showed no foetal malformations in rats at 50mg/kg [121], 7 out of 9 identified studies documented adverse effects after prenatal gabapentin exposure. Some of these adverse outcomes included foetal resorptions [121–124], low foetal weight [122–124] and reduced crown-rump length [124] at doses ranging from 20 to 452 mg/kg (i.p. injection).

In Prakash et al. (2008) mice were administered gabapentin at three different doses (113 mg/kg, 226mg/kg, 452 mg/kg; i.p. injection), equivalent to low, middle and high range in humans, and at three different gestational stages (early, mid or late gestation) [124]. This study evidenced various gross anomalies when administered mid-gestation at all three doses, with the incidence of gross malformations increasing with increasing dose. These malformations included brachygnathia, pointed snout, cataracts, shortened necks and limb deformities [124]. Further, other mouse studies of lower gabapentin doses (20–50 mg/kg, i.p. injection, GD 1–10 and GD 0–15) support these outcomes, producing brachygnathia [123], limb deformities [122, 123], vertebral column deformities, exencephaly, severe trunk malformations, mandibular hypoplasia and delayed ossification [123].

A common finding among two studies, one mouse model [122] and one chick embryo model [125] highlighted the negative impact of prenatal gabapentin exposure on neural tube closure [122, 125], suggesting potential implications for neural tube defects such as spina bifida. One mouse model of free access gabapentin exposure (30 mg/kg) mid-pregnancy showed no difference in grown offspring weight compared to controls; however, gabapentin-exposed dams had significantly lower body weights at postpartum day 21 [126].

Examining the neurotoxic effects of gabapentin during prenatal exposure, Erisgin et al. (2017) reported no adverse impact on the rat brain at a dose (50 mg/kg/day, oral gavage) equivalent to a low human dose [127]. Similarly, another investigation found that while there was no change in rat brain weight with the same dose and administration, there was an increase in the total number of neurons [121]. In contrast, a rat model of a higher gabapentin dose (162 mg/kg/day, i.p. injection), equivalent to a mid-range dose in adult humans, revealed a significant decrease in foetal brain weight compared with water controls [128]. This higher dose induced neurodegenerative apoptosis in the cerebral cortical and hippocampal regions. Additionally, research by Prakash et al. (2008) illustrated reduced foetal brain size and distorted brain shape with a comparable gabapentin dose of 113 mg/kg/day (i.p. injection) during mid and late gestation [124]. They found the incidence of reduced foetal brain weight increased with increasing doses from 113 to 452 mg/kg.

4 Discussion

Research into the safety of alcohol pharmacotherapies in pregnancy is incredibly limited, particularly given the known harms associated with the use of alcohol during pregnancy. There is a notable gap in understanding and many studies present conflicting findings. While 105 papers were identified, only 3.8% examined the safety of medication of interest in the context of AUD. This is concerning considering the well-established teratogenic effects of prenatal alcohol exposure [8, 9] and the prevalence of alcohol consumption in pregnancy [1].

There is growing evidence, particularly in patients with opioid use disorders, that naltrexone is not associated with substantial negative outcomes for either mother or neonate. Compared with neonates exposed to methadone or buprenorphine, naltrexone exposed infants had lower rates of NAS and hospitalisation [25, 26], with two case series and a brief communication finding normal obstetric and birth outcomes [19–21]. However, the research thus far has highlighted some areas that warrant further investigation, including the increased risk of urogenital congenital anomalies [23] and ectopic pregnancies [22]. Furthermore, owing to the many differences between opioid use disorders and AUD in terms of additional illicit drug use and comorbidities [129], a better understanding of the safety of naltrexone in the treatment of AUD is vital.

While very minimal research has been conducted on the safety of acamprosate in pregnancy, preliminary evidence has suggested little cause for concern. In the few studies conducted, there were no adverse effects associated with prenatal acamprosate exposure [41–43]; however, only one of these studies was conducted in humans [42]. While the small case-series in France reported spontaneous abortions and infants with congenital anomalies, concurrent exposure to alcohol and other drugs makes it impossible to delineate if these effects are associated with acamprosate alone [44]. Further research should focus on the safety of acamprosate in humans, especially considering it is a first line pharmacotherapy for the treatment of AUD in Australia, Europe and the USA.

Although there was an absence of safety data on the use of disulfiram in pregnancy, historical research suggests some serious concerns. Disulfiram is thought to be harmful in pregnancy due to two main reasons. Firstly, disulfiram acts as a copper chelating agent, lowering blood and tissue copper levels which can harm the pregnancy and the exposed neonate causing early embryonic death, congenital anomalies and impaired cognitive and behavioural function [130, 131]. Additionally, as per the medication's method of action, the combination of disulfiram and alcohol together causes severe autonomic instability (e.g. heart palpitations, dizziness etc.) which is a risk to the pregnant mother and their developing fetus [132]. For these reasons, it is suggested disulfiram be avoided during pregnancy.

Even though baclofen is typically only used off-label for the treatment of AUD (apart from its more recent approval in France [133]) and is more commonly used for the treatment of muscle spasticity, it was interesting to see very limited research into its safety in pregnancy for either indication. The few animal studies investigating baclofen's safety in pregnancy indicate a risk of neural tube defects [53, 54], which would be an important starting place for research clinically.

Our search found no human or animal studies investigating the safety of nalmefene in pregnancy. The lack of literature may be attributed to nalmefene's indication for opioid overdose, as well as its turbulent approval history. Historically, nalmefene has only been used as an antidote for opioid overdose (via a single administration) [134]. As such, its safety in pregnancy has not been a research priority. In terms of its use for the treatment of AUD, nalmefene was produced in tablet form and approved by the EMA in 2013 [135]. However, this oral formulation of the drug is not yet approved by the FDA in the USA and is therefore unavailable [136]. Nalmefene tablets were approved by the TGA in Australia for the treatment of AUD in 2016 [137]; however, in 2019 the registration was discontinued by the pharmaceutical company [138], rendering the medication unavailable in Australia. With this, it is perhaps understandable that research has not focussed on the medication's safety in pregnancy, especially when its primary indication was to reverse opioid overdose, and it is yet to be approved for the treatment of AUD in many countries. However, since the oral formulation of nalmefene is approved for AUD treatment in Europe, and there is potential for other countries to follow suit, it is increasingly important to investigate its safety in pregnant individuals.

Several concerns regarding the use of topiramate and gabapentin in pregnancy have been identified. For topiramate, studies raise concerns regarding its impact on congenital anomalies (particularly oral clefts) [55–70, 75] and foetal growth [60, 74, 83, 86–88]. While topiramate is an antiseizure medication, it is also used for weight management. It is therefore possible that topiramate induced weight loss during pregnancy may mediate the medication's impact on foetal growth. Although gabapentin was not found to have an increased risk of major congenital anomalies [57, 65, 68, 72, 73, 81, 83, 91, 110, 111, 113–115, 139], multiple studies noted an increased risk of preterm birth, small size for gestational age and NICU admission [110–112]. While the safety of topiramate and gabapentin in pregnancy has been very well studied, no studies were in the context of AUD; most research focussed on their use as antiseizure medications. Due to the substantial degree of inconsistency and identified risk, very careful consideration is needed when contemplating topiramate or gabapentin as medications to treat AUD in pregnancy.

4.1 Limitations

Some limitations should be noted. First, in this review we included studies where the medications of interest were used in pregnancy for the treatment of indications other than AUD. While these studies provide important information about the safety of these medications in pregnancy, outcomes in women with AUD may differ. The main disadvantage of this is that other factors, such as seizures for epileptic patients, may impact pregnancy and neonatal outcomes irrespective of medications used. This issue further emphasizes the need for more comprehensive research on the safety of alcohol pharmacotherapies in pregnancy in the context of AUD. It is of note, the use of some medications in pregnancy need consideration beyond their safety profile. Both naltrexone and nalmefene are opioid antagonists and therefore there are some complications with the administration of opioid pain relief during labour, particularly following caesarean sections [140]. Care needs to be given when providing treatment to patients, non-opioid alternatives exist and should be considered. Additionally, the review failed to consider the efficacy of the medications in pregnancy. However, research into medication efficacy in pregnancy continues to be extremely rare, particularly for AUD [141].

4.2 Clinical Problem

The treatment of pregnant individuals with AUD poses a complex challenge for healthcare providers, as they must carefully weigh the potential risks and benefits of intervention. While research into medication safety in pregnancy is often neglected due to the high risk of harm, the reluctance to treat pregnant individuals due to the unknown safety of medications raises concerns, particularly in the context of the known extremely teratogenic effects of alcohol. The risk of the teratogenic effects of alcohol must be balanced against the potential risks associated with the medications to treat AUD. Avoiding potential harm from the medications is challenging since the safety of such medications has not been established in pregnancy. The limited data on the safety of alcohol pharmacotherapies in pregnancy, as evidenced in this review, makes risk assessment challenging. However, balancing the risk of untreated AUD against the potential medication-related risks is crucial to provide care for both the pregnant individual and the developing child.

5 Conclusion

Evidence regarding the safety of alcohol pharmacotherapies in pregnancy is substantially lacking and often contradictory. Further research, particularly in the context of AUD, is essential to comprehensively understand the potential benefits or risks associated with alcohol pharmacotherapy use in pregnancy. Based on the currently available data, and the known teratogenic effects of alcohol exposure, naltrexone would likely be the first to be considered in the treatment of AUD in pregnancy. At present, there is limited and mixed information on the safety of acamprosate in pregnancy, inadequate information for baclofen and no data for nalmefene. The use of disulfiram should be avoided in pregnancy due to the risk of congenital anomalies, as well as medications with better established safety profiles. Where possible, it is advisable to consider alternative pharmacotherapies instead of using topiramate and gabapentin in pregnancy due to the risk of foetal harm. Careful consideration of the potential risks and benefits needs to be weighed up before any alcohol pharmacotherapy is used in pregnancy. Future research on both the safety and efficacy of medications to treat AUD in pregnancy will enable healthcare providers and pregnant individuals to make informed decisions, as well as guide policy makers.

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Ebony Quintrell and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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